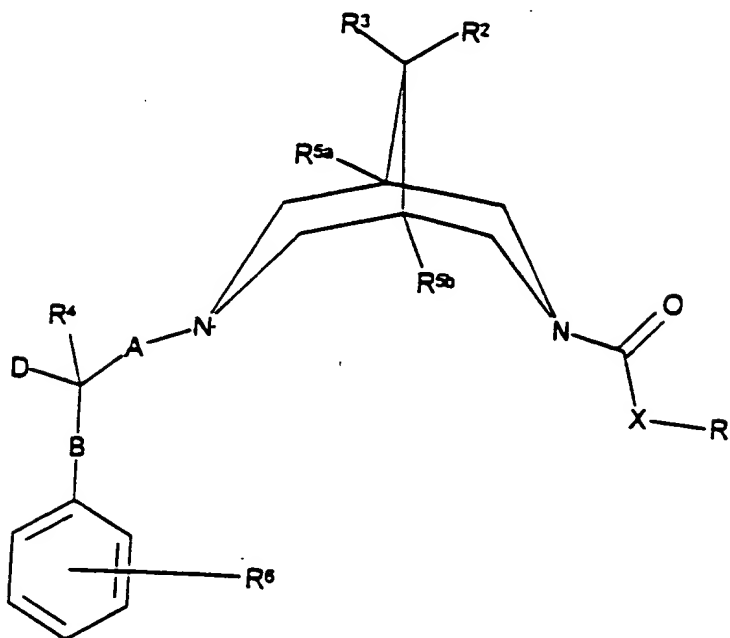


AMENDMENTS TO THE CLAIMS

Please substitute the following amended claims for corresponding claims previously presented.

1 (Currently amended). A compound of formula I,



wherein

R¹ represents C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, -(CH₂)_a-aryl, or (CH₂)_aHet¹ (all of which are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and/or C₁₋₄ alkoxy or C₃₋₄ cycloalkoxy);

a represents 0, 1, 2, 3, or 4;

Het¹ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a} and R^{5b} independently represent H or C₁₋₃ alkyl or C₃ cycloalkoxy;

R² and R³ independently represent H, C₁₋₄ alkyl (optionally substituted with one or more nitro or cyano groups), C₃₋₄ cycloalkyl, OR⁷, N(R^{7a})R^{7b}, OC(O)R⁸ or together form -O-(CH₂)₂-O-, -(CH₂)₃-, -(CH₂)₄- or -(CH₂)₅-;

R⁷ and R⁸ independently represent H, C₁₋₆ alkyl, or -(CH₂)_b-aryl or C₃₋₆ cycloalkoxy (which latter ~~two~~ three groups are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C₁₋₄ alkyl, and/or C₁₋₄ alkoxy, C₃₋₄ cycloalkyl and/or C₃₋₄ cycloalkoxy);

R^{7a} and R^{7b} independently represent H, or C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

b represents 0, 1, 2, 3 or 4;

R⁴ represents H, or C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

D represents H, -OH, or -(CH₂)_cN(R¹⁰)(R¹¹);

c represents 0, 1, 2, 3 or 4;

R¹⁰ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -(CH₂)_d-aryl, -C(NH)NH₂, -S(O)₂R¹³, -[C(O)]_eN(R¹⁴)(R¹⁵), -C(O)R¹⁶ or -C(O)OR¹⁷;

e represents 1 or 2;

R¹¹ represents H, C₁₋₆ alkyl, -C(O)R¹⁸ or -(CH₂)_f-aryl (which latter group is optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

R^{14} , R^{15} , R^{16} , R^{17} and R^{18} independently represent H, C_{1-6} alkyl, C_{3-6} cycloalkyl, Het^2 or $-(CH_2)_g$ -aryl (which latter three groups are optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy, C_{3-6} cycloalkyl and/or C_{3-6} cycloalkoxy);

R^{13} represents C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl or $-(CH_2)_h$ -aryl (all of which are all optionally substituted by one or more substituents chosen from halo, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy, C_{3-6} cycloalkyl and/or C_{3-6} cycloalkoxy);

d, f, g and h independently represent 0, 1, 2, 3 or 4;

Het^2 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^6 represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl (optionally terminated by $-N(H)C(O)OR^{18a}$), C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, $-C(O)N(H)R^{19}$, $-NHC(O)N(H)R^{20}$, $-N(H)S(O)_2R^{21}$ and/or $-OS(O)_2R^{22}$;

R^{19} and R^{20} independently represent H or C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^{18a} , R^{21} and R^{22} independently represent C_{1-6} alkyl or C_{3-6} cycloalkyl;

A represents a single bond, C_{1-6} alkylene, $-N(R^{23})(CH_2)_j-$, $-O(CH_2)_j-$ or $-(CH_2)_jC(H)(OR^{23})(CH_2)_k-$ (in which latter three groups, the $-(CH_2)_j-$ group is attached to the bispidine nitrogen atom, and which latter four groups are all optionally substituted by one or more OH groups);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_mN(R^{24})-$, $(CH_2)_mS(O)_n-$, $-(CH_2)_mO-$ (in which three latter groups, the $-(CH_2)_m-$ group is attached to the carbon atom bearing D and R^4), $-C(O)N(R^{24})-$ (in which latter group, the $-C(O)-$ group is

attached to the carbon atom bearing D and R⁴), N(R²⁴)C(O)O(CH₂)_m- or -N(R²⁴)(CH₂)_m- (in which latter two groups, the N(R²⁴) group is attached to the carbon atom bearing D and R⁴);

j, k and m independently represent 0, 1, 2, 3 or 4;

n represents 0, 1 or 2;

R²³ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or C(O)R²⁵

R²⁴ represents H or C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R²⁵ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Het³ or -(CH₂)_p-aryl (which latter two groups are optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

Het³ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

p represents 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, N-oxide or C₁₋₄ alkyl quaternary ammonium derivative thereof;

wherein alkyl groups that R¹, R², R³, R⁴, R^{5a}, R^{5b}, R⁶, R⁷, R^{7a}, R^{7b}, R⁸, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R^{18a}, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵ and D may represent, and with which R¹, R⁷, R⁸, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R²⁵ may be substituted; and alkoxy groups and R⁶ may represent, and with which R¹, R⁷, R⁸, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R²⁵ may be substituted, may be linear or, when there is a sufficient number (i.e. three) of carbon atoms, be branched and/or cyclic, and wherein, when there is a sufficient number (i.e. four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic, and wherein such alkyl and alkoxy groups may also be

saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen and/or substituted by one or more fluoro groups; and

wherein alkylene groups that A and B may represent, and $-(CH_2)-$ containing groups that R^1 , R^2 and R^3 (together), R^7 , R^8 , R^{10} , R^{11} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{25} , A, B and D may include, may be linear or, when there is a sufficient number (i.e. two) of carbon atoms, be branched, and wherein such alkylene groups and $-(CH_2)-$ containing chains may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen;

provided that:

(a) when D represents either H or $-OH$, and R^{5a} and R^{5b} both represent H, then at least one of R^2 and R^3 represents OR^7 , $OC(O)R^8$ or C_{1-4} alkyl, which alkyl group is substituted with one or more nitro or cyano groups; and

(b) when D represents $-OH$ or $-(CH_2)_cN(R^{10})R^{11}$ in which c represents 0, then:-

(i) A does not represent $-N(R^{23})(CH_2)_j-$, $-O(CH_2)_j-$ or $-CH_2)_jC(H)(OR^{23})(CH_2)_k-$ (in which k is 0); and/or

(ii) m does not represent 0 when B represents $-(CH_2)_mN(R^{24})-$, $-(CH_2)_mS(O)_n-$ or $-(CH_2)_mO-$.

2 (previously amended). A compound as claimed in Claim 1, wherein R^1 represents optionally substituted $-(CH_2)_a$ -phenyl, in which a is 0, 1, 2 or 3, or optionally substituted, optionally unsaturated, linear, branched or cyclic, C_{1-18} alkyl (which latter group may also be interrupted by an oxygen atom).

3 (previously amended). A compound as claimed in Claim 1, wherein R^2 represents H, OR^7 , $-CH_2NO_2$ or $-OC(O)R^8$ or together with R^3 $-O-(CH_2)_2-O-$.

4 (previously amended). A compound as claimed in Claim 1, wherein R^3 represents H, OR^7 , C_{1-4} alkyl or together with R^2 represents $-O-(CH_2)_2-O-$.

5 (previously amended). A compound as claimed in Claim 1, wherein R^4 represents H or C_{1-2} alkyl.

6 (previously amended). A compound as claimed in Claim 1, wherein R^{5a} and R^{5b} either both represent H or both represent methyl.

7 (previously amended). A compound as claimed in Claim 1, wherein R^6 represents one or more substituents selected from C_{1-6} alkyl, cyano, nitro, amino or $C(O)N(H)R^{19}$ or $N(H)S(O)_2R^{21}$.

8 (previously amended). A compound as claimed in Claim 1, wherein X represents O.

9 (previously amended). A compound as claimed in Claim 1, wherein A represents a single bond or linear, or branched, C_{1-4} alkylene (which group is also optionally interrupted by O).

10 (previously amended). A compound as claimed in Claim 1, wherein B represents a single bond, C₁₋₄ alkylene, -(CH₂)_mO- or -(CH₂)_mN(R²⁴)- (in which latter two cases m is 1, 2 or 3).

11 (previously amended). A compound as claimed in Claim 1, wherein when D represents -(CH₂)_cN(R¹⁰)(R¹¹), c represents 0, 1 or 2.

12 (previously amended). A compound as claimed in Claim 1, wherein when D represents -(CH₂)_cN(R¹⁰)(R¹¹), R¹⁰ represents H, C₁₋₄ alkyl, -C(O)R¹⁶ (in which R¹⁶ is H, C₁₋₃ alkyl or Het²), -C(O)OR¹⁷ (in which R¹⁷ is C₁₋₅ alkyl, phenyl or C₁₋₃ alkylphenyl), -C(NH)NH₂ or [C(O)]_eN(H)R₁₅ (in which R₁₅ is H or C₁₋₃ alkyl).

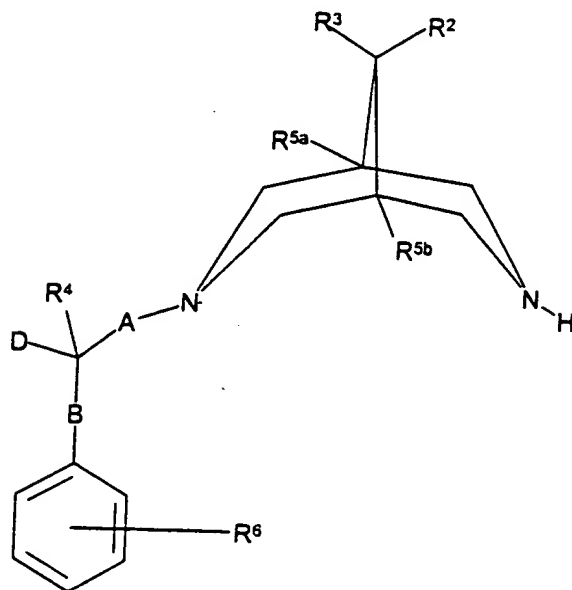
13 (previously amended). A compound as claimed in Claim 1, wherein when D represents -(CH)_cN(R¹⁰)(R¹¹), R¹¹ represents H.

14 (previously amended). A pharmaceutical formulation including a compound as defined in Claim 1 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

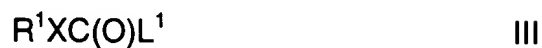
20 (currently amended). A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in Claim 1 to a person ~~suffering from or susceptible to, such a~~ condition in need thereof.

21 (currently amended) A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:

(a) reaction of a compound of formula II,

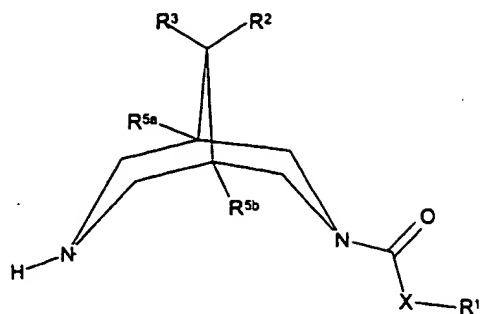


wherein R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^6 , A, B and D are as defined in Claim 1 with a compound of formula III,



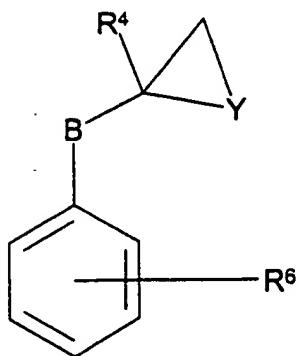
wherein L^1 represents a leaving group and R^1 and X are as defined in Claim 1;

(b) for compounds of formula I in which A represents CH_2 and D represents $-OH$ or $N(R^{10})H$, reaction of a compound of formula IV,



IV

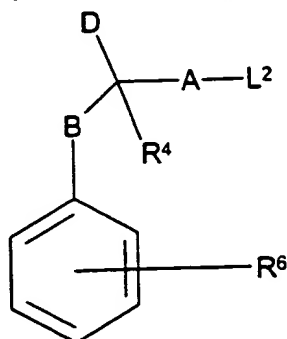
wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} and X are as defined in Claim 1, with a compound of formula V,



V

wherein Y represents O or $N(R^{10})$ and R^4 , R^6 , R^{10} and B are as defined in Claim 1;

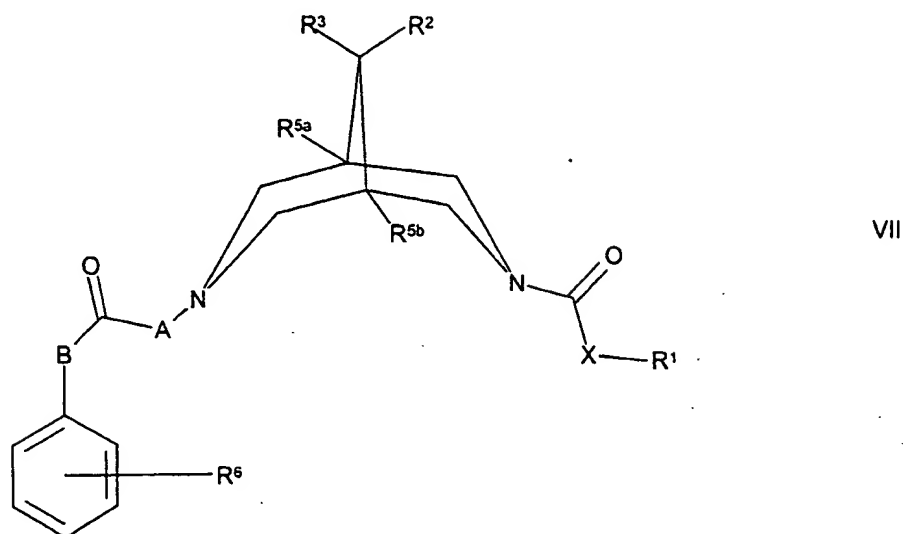
(c) reaction of a compound of formula IV, as defined above, with a compound of formula VI,



VI

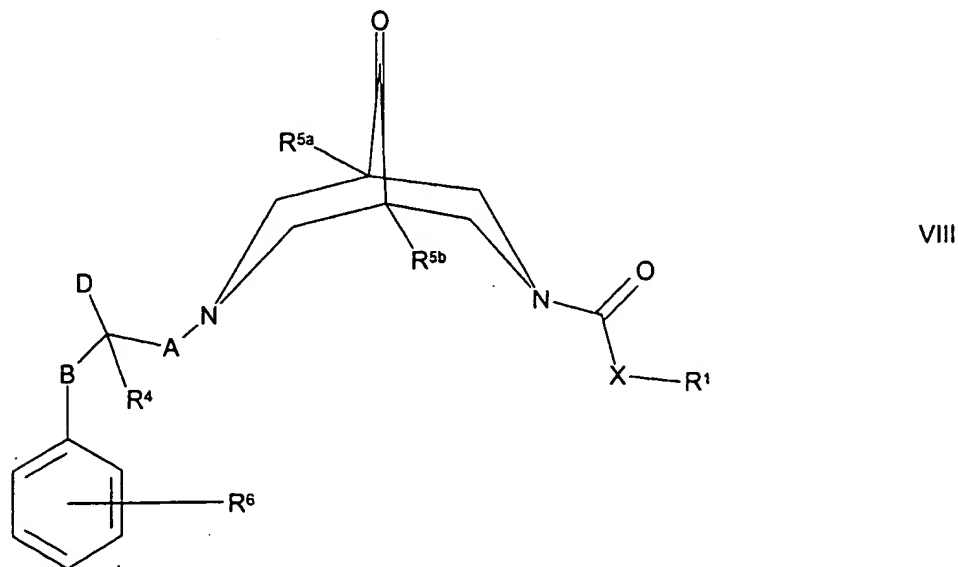
wherein L^2 represents a leaving group and R^4 , R^6 , A , B and D are as defined in Claim 1;

(d) for compounds of formula I in which D represents H or OH and R^4 represents H, reduction of a compound of formula VII,



wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^6 , A, B and X are as defined in Claim 1;

(e) for compounds of formula I in which one of R^2 and R^3 represents H or OH and the other represents H, reduction of a corresponding compound of formula VIII,



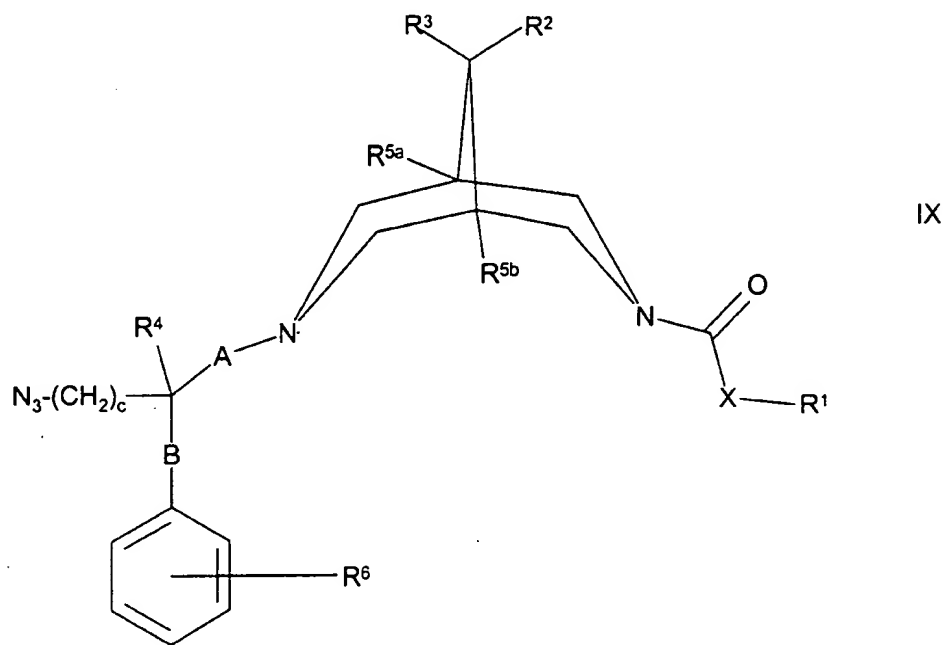
wherein R^1 , R^4 , R^{5a} , R^{5b} , R^6 , A, B, D and X are as defined in Claim 1;

(f) for compounds of formula I in which R^2 and/or R^3 represents $OC(O)R^8$ and R^8 is as defined in Claim 1, coupling of a corresponding compound of formula I in which R^2 and/or R^3 (as appropriate) represents OH and a compound of formula VIIIA,



wherein R^8 is as defined in Claim 1;

(g) for compounds of formula I in which D represents $-(CH_2)_cNH_2$, reduction of a corresponding compound of formula IX,



wherein c , R^1 , R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^6 , A, B and X are as defined in Claim 1;

(h) for compounds of formula I in which D represents $-N(R^{11})C(O)NH(R^{15})$, in which R^{11} and R^{15} are as defined in Claim 1 except that R^{11} does not represent $C(O)R^{18}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as defined in Claim 1 except that it does not represent $C(O)R^{18}$ in which R^{18} is as defined in Claim 1, with a compound of formula X,



wherein R^{15} is as defined in Claim 1;

(i) for compounds of formula I in which D represents $-\text{N}(\text{H})[\text{C}(\text{O})]_2\text{NH}_2$, reaction of a corresponding compound of formula I in which D represents

$-\text{NH}_2$ with oxalic acid diamide;

(j) for compounds of formula I in which D represents $-\text{N}(\text{R}^{11})\text{C}(\text{O})\text{R}^{16}$, in which R^{11} and R^{16} are as defined in Claim 1 except that R^{11} does not represent $\text{C}(\text{O})\text{R}^{18}$, reaction of a corresponding compound of formula I in which D represents $-\text{N}(\text{R}^{11})\text{H}$, in which R^{11} is as defined in Claim 1 except that it does not represent $\text{C}(\text{O})\text{R}^{18}$ in which R^{18} is as defined in Claim 1, with a compound of formula XI,



wherein R_x represents a suitable leaving group and R^{16} is as defined in Claim 1;

(k) for compounds of formula I in which D represents $-\text{N}(\text{H})\text{R}^{10}$ and R^{10} is as defined in Claim 1 except that it does not represent H or $-\text{C}(\text{NH})\text{NH}_2$, reaction of a corresponding compound of formula I wherein D represents $-\text{NH}_2$ with a compound of formula XIA,



wherein R^{10a} represents R^{10} as defined in Claim 1 except that it does not represent H or $-\text{C}(\text{NH})\text{NH}_2$ and L^1 is as defined above;

(l) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I;

(m) for compounds of formula I which are C_{1-4} alkyl quaternary ammonium salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of

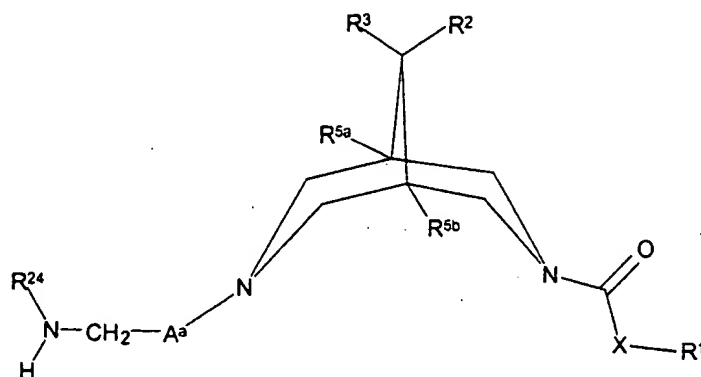
formula XII,



XII

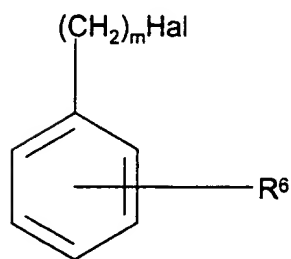
wherein R^a represents C_{1-4} alkyl and Hal represents Cl, Br or I;

(n) for compounds of formula I in which D and R^4 both represent H, A represents C_{1-6} alkylene, B represents $N(R^{24})(CH_2)_m$ and m and R^{24} are as defined in Claim 1, reaction of a compound of formula XIII,



XIII

wherein A^a represents C_{1-6} alkylene and R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^{24} and X are as defined in Claim 1 with a compound of formula XIV,



XIV

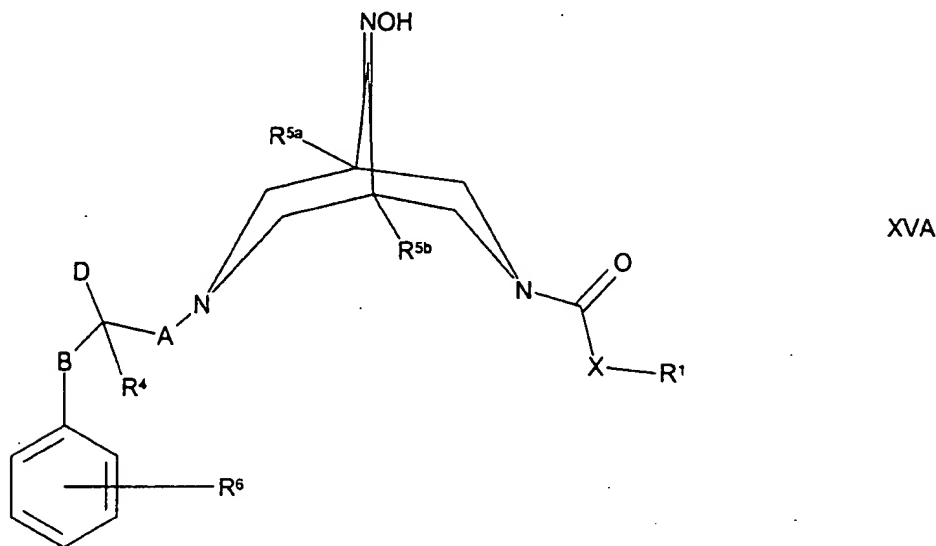
wherein R^6 , m are as defined in Claim 1 and Hal is as defined above;

(o) reaction of a compound of formula II, as defined above, with a compound of formula XV,



XV

wherein R^1 and X are as defined in Claim 1, in the presence of 1,1'-carbonyldiimidazole;
 (p) for compounds of formula I in which one of R^2 and R^3 represents $-\text{NH}_2$ and the other represents H, reduction of a compound of formula XVA,



wherein R^1 , R^4 , R^{5a} , R^{5b} , R^6 , A, B, D and X are as defined in Claim 1; or

(q) for compounds of formula I in which one or both of R^2 and R^3 represent $-\text{N}(\text{R}^{7a})\text{R}^{7b}$ in which one or both of R^{7a} and R^{7b} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^2 and/or R^3 represent $-\text{N}(\text{R}^{7a})\text{R}^{7b}$ (as appropriate) in which R^{7a} and/or R^{7b} (as appropriate) represent H, using a compound of formula XXIB,

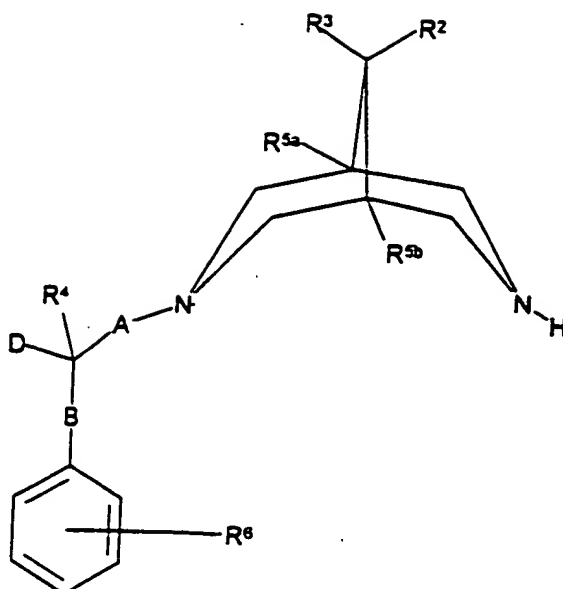


wherein R^{7c} represents C_{1-6} alkyl and L^1 is as defined above; or

(r) conversion of one R^6 substituent to another; or

~~(s) (r) deprotection of a protected derivative of a compound of formula I as defined in Claim 1.~~

22 (currently amended). A compound of formula II



II

wherein R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^6 , A, B and D are as defined in Claim 1

R^{5a} and R^{5b} independently represent H, C_{1-3} alkyl or C_3 cycloalkoxy;

R^2 and R^3 independently represent H, C_{1-4} alkyl (optionally substituted with one or more nitro or cyano groups), C_{3-4} cycloalkyl, OR^7 , $N(R^{7a})R^{7b}$, $OC(O)R^8$ or together form -
 $O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;

R^7 and R^8 independently represent H, C_{1-6} alkyl, $-(CH_2)_b$ -aryl or C_{3-6} cycloalkoxy
 (which latter three groups are optionally substituted by one or more substituents
 selected from -OH, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-4} cycloalkyl and/or C_{3-4}
 cycloalkoxy);

R^{7a} and R^{7b} independently represent H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

b represents 0, 1, 2, 3 or 4;

R^4 represents H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

D represents H, -OH, or $-(CH_2)_cN(R^{10})(R^{11})$;

c represents 0, 1, 2, 3 or 4;

R¹⁰ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -(CH₂)_d-aryl, -C(NH)NH₂, -S(O)₂R¹³, -[C(O)]_eN(R¹⁴)(R¹⁵), -C(O)R¹⁶ or -C(O)OR¹⁷;

e represents 1 or 2;

R¹¹ represents H, C₁₋₆ alkyl, -C(O)R¹⁸ or -(CH₂)_f-aryl (which latter group is optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ independently represent H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Het² or -(CH₂)_g-aryl (which latter three groups are optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

R¹³ represents C₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl or -(CH₂)_h-aryl (all of which are all optionally substituted by one or more substituents chosen from halo, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

d, f, g and h independently represent 0, 1, 2, 3 or 4;

Het² represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R⁶ represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl (optionally terminated by -N(H)C(O)OR^{18a}), C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, -C(O)N(H)R¹⁹, -NHC(O)N(H)R²⁰, -N(H)S(O)₂R²¹ and/or -OS(O)₂R²²;

R¹⁹ and R²⁰ independently represent H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R^{18a}, R²¹ and R²² independently represent C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

A represents a single bond, C₁₋₆ alkylene, -N(R²³)(CH₂)_j-, -O(CH₂)_j- or -(CH₂)_jC(H)(OR²³)(CH₂)_k- (in which latter three groups, the -(CH₂)_j- group is attached to the bispidine nitrogen atom, and which latter four groups are all optionally substituted by one or more OH groups);

B represents a single bond, C₁₋₄ alkylene, -(CH₂)_mN(R²⁴)-, (CH₂)_mS(O)_n-, -(CH₂)_mO- (in which three latter groups, the -(CH₂)_m- group is attached to the carbon atom bearing D and R⁴), -C(O)N(R²⁴)- (in which latter group, the -C(O)- group is attached to the carbon atom bearing D and R⁴), N(R²⁴)C(O)O(CH₂)_m- or -N(R²⁴)(CH₂)_m- (in which latter two groups, the N(R²⁴) group is attached to the carbon atom bearing D and R⁴);

j, k and m independently represent 0, 1, 2, 3 or 4;

n represents 0, 1 or 2;

R²³ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or C(O)R²⁵

R²⁴ represents H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R²⁵ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Het³ or -(CH₂)_p-aryl (which latter two groups are optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

Het³ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

p represents 0, 1, 2, 3 or 4;

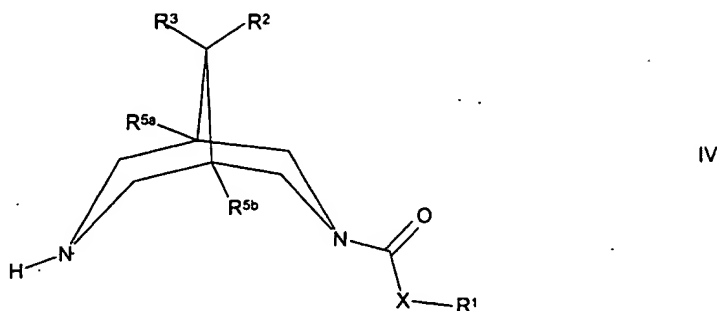
wherein alkyl groups that R², R³, R⁴, R^{5a}, R^{5b}, R⁶, R⁷, R^{7a}, R^{7b}, R⁸, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R^{18a}, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵ and D may represent, and with which R⁷, R⁸, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R²⁵ may be substituted; and

alkoxy groups and R^6 may represent, and with which R^7 , R^8 , R^{11} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{25} may be substituted, may be linear or, when there is a sufficient number (i.e. three) of carbon atoms, be branched and/or cyclic, and wherein, when there is a sufficient number (i.e. four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic, and wherein such alkyl and alkoxy groups may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen and/or substituted by one or more fluoro groups; and

wherein alkylene groups that A and B may represent, and $-(CH_2)-$ containing groups that R^2 and R^3 (together), R^7 , R^8 , R^{10} , R^{11} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{25} , A, B and D may include, may be linear or, when there is a sufficient number (i.e. two) of carbon atoms, be branched, and wherein such alkylene groups and $-(CH_2)-$ containing chains may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen,

or a derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then D does not represent H or OH.

23 (currently amended). A compound of formula IV



wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} and X are as defined in Claim 1

R¹ represents C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, -(CH₂)_a-aryl, or (CH₂)_aHet¹ (all of which are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and/or C₁₋₄ alkoxy or C₃₋₄ cycloalkoxy);

a represents 0, 1, 2, 3, or 4;

Het¹ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a} and R^{5b} independently represent H, C₁₋₃ alkyl or C₃ cycloalkoxy;

R² and R³ independently represent H, C₁₋₄ alkyl (optionally substituted with one or more nitro or cyano groups), C₃₋₄ cycloalkyl, OR⁷, N(R^{7a})R^{7b}, OC(O)R⁸ or together form -O-(CH₂)₂-O-, -(CH₂)₃-, -(CH₂)₄- or -(CH₂)₅-;

R⁷ and R⁸ independently represent H, C₁₋₆ alkyl, -(CH₂)_b-aryl or C₃₋₆ cycloalkoxy (which latter three groups are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C₁₋₄ alkyl, r C₁₋₄ alkoxy, C₃₋₄ cycloalkyl and/or C₃₋₄ cycloalkoxy);

R^{7a} and R^{7b} independently represent H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

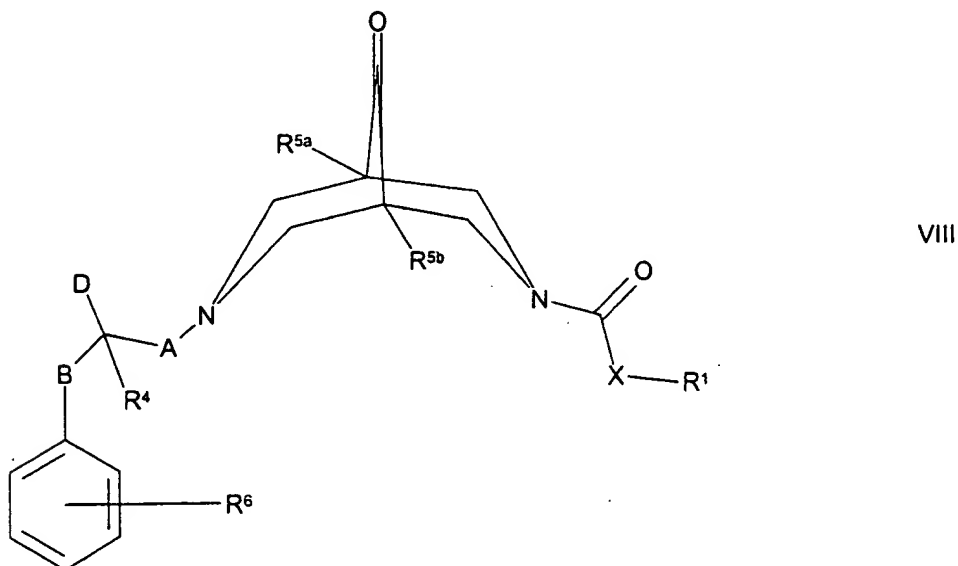
b represents 0, 1, 2, 3 or 4;

wherein alkyl groups that R¹, R², R³, R^{5a}, R^{5b}, R⁷, R^{7a}, R^{7b} and R⁸ may represent, and with which R¹, R⁷ and R⁸ may be substituted; and alkoxy groups and with which R¹, R⁷ and R⁸ may be substituted, may be linear or, when there is a sufficient number (i.e. three) of carbon atoms, be branched and/or cyclic, and wherein, when there is a sufficient number (i.e. four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic, and wherein such alkyl and alkoxy groups may also be saturated or,

when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen and/or substituted by one or more fluoro groups;

or a derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then at least one of R^2 and R^3 represents OR^7 , $OC(O)R^8$ or C_{1-4} alkyl, which alkyl group is substituted with one or more nitro or cyano groups.

24 (currently amended). A compound of formula VIII



wherein R^1 , R^4 , R^{5a} , R^{5b} , R^6 , A, B, D and X are as defined in Claim 1

R^1 represents C_{1-12} alkyl, C_{3-12} cycloalkyl, $-(CH_2)_a$ -aryl, or $(CH_2)_a$ Het¹ (all of which are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl, C_{3-4} cycloalkyl and/or C_{1-4} alkoxy or C_{3-4} cycloalkoxy);

a represents 0, 1, 2, 3, or 4;

Het¹ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a} and R^{5b} independently represent H, C₁₋₃ alkyl or C₃ cycloalkoxy;

R⁴ represents H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

D represents H, -OH, or -(CH₂)_cN(R¹⁰)(R¹¹);

c represents 0, 1, 2, 3 or 4;

R¹⁰ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -(CH₂)_d-aryl, -C(NH)NH₂, -S(O)₂R¹³, -[C(O)]_eN(R¹⁴)(R¹⁵), -C(O)R¹⁶ or -C(O)OR¹⁷;

e represents 1 or 2;

R¹¹ represents H, C₁₋₆ alkyl, -C(O)R¹⁸ or -(CH₂)_f-aryl (which latter group is optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ independently represent H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Het² or -(CH₂)_g-aryl (which latter three groups are optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

R¹³ represents C₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl or -(CH₂)_h-aryl (all of which are all optionally substituted by one or more substituents chosen from halo, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

d, f, g and h independently represent 0, 1, 2, 3 or 4;

Het² represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R⁶ represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl (optionally terminated by -N(H)C(O)OR^{18a}), C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, -C(O)N(H)R¹⁹, -NHC(O)N(H)R²⁰, -N(H)S(O)₂R²¹ and/or -OS(O)₂R²²;

R¹⁹ and R²⁰ independently represent H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R^{18a}, R²¹ and R²² independently represent C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

A represents a single bond, C₁₋₆ alkylene, -N(R²³)(CH₂)_i-, -O(CH₂)_j- or -(CH₂)_lC(H)(OR²³)(CH₂)_k- (in which latter three groups, the -(CH₂)_j- group is attached to the bispidine nitrogen atom, and which latter four groups are all optionally substituted by one or more OH groups);

B represents a single bond, C₁₋₄ alkylene, -(CH₂)_mN(R²⁴)-, (CH₂)_mS(O)_n-, -(CH₂)_mO- (in which three latter groups, the -(CH₂)_m- group is attached to the carbon atom bearing D and R⁴), -C(O)N(R²⁴)- (in which latter group, the -C(O)- group is attached to the carbon atom bearing D and R⁴), N(R²⁴)C(O)O(CH₂)_m- or -N(R²⁴)(CH₂)_m- (in which latter two groups, the N(R²⁴) group is attached to the carbon atom bearing D and R⁴);

i, k and m independently represent 0, 1, 2, 3 or 4;

n represents 0, 1 or 2;

R²³ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or C(O)R²⁵

R²⁴ represents H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R²⁵ represents H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Het³ or -(CH₂)_p-aryl (which latter two groups are optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl and/or C₃₋₆ cycloalkoxy);

Het³ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

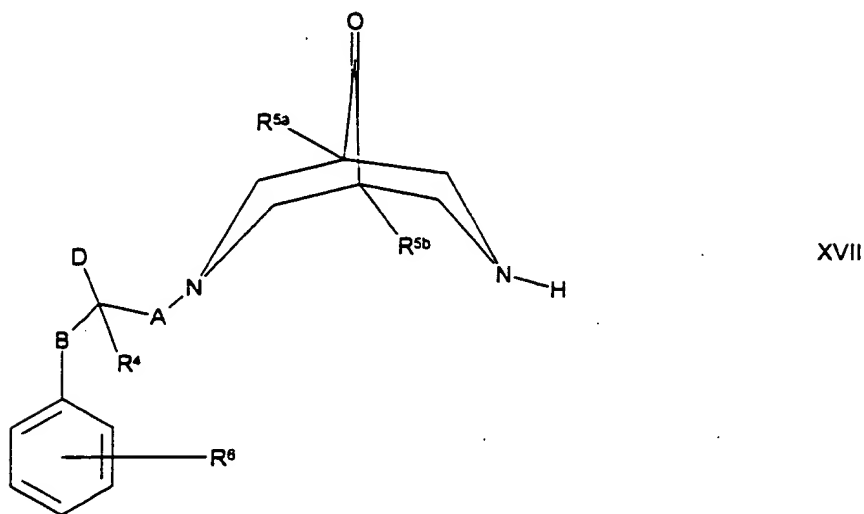
p represents 0, 1, 2, 3 or 4;

wherein alkyl groups that R¹, R⁴, R^{5a}, R^{5b}, R⁶, R⁷, R^{7a}, R^{7b}, R⁸, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R^{18a}, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵ and D may represent, and with which R¹, R⁷, R⁸, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R²⁵ may be substituted; and alkoxy groups and R⁶ may represent, and with which R¹, R⁷, R⁸, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R²⁵ may be substituted, may be linear or, when there is a sufficient number (i.e. three) of carbon atoms, be branched and/or cyclic, and wherein, when there is a sufficient number (i.e. four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic, and wherein such alkyl and alkoxy groups may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen and/or substituted by one or more fluoro groups; and

wherein alkylene groups that A and B may represent, and -(CH₂)- containing groups that R¹, R⁷, R⁸, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R²⁵, A, B and D may include, may be linear or, when there is a sufficient number (i.e. two) of carbon atoms, be branched, and wherein such alkylene groups and -(CH₂)- containing chains may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen,

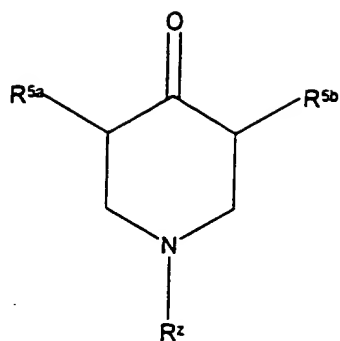
or a derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then D does not represent H or OH.

25 (previously presented). A compound of formula XVII,



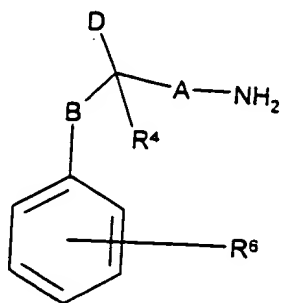
wherein R^4 , R^{5a} , R^{5b} , R^6 , A, B and D are as defined in Claim 1, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then D does not represent H or OH.

26 (currently amended). A process for the preparation of a compound of formula VIII, as defined in Claim 24, or a compound of formula XVII, as defined in Claim 25, which comprises reaction of a compound of formula XXIX,



XXIX

wherein R^z represents H or $-C(O)XR^1$ and R^1 , R^{5a} , R^{5b} and X are as defined in Claim 1 with a compound of formula XXX,

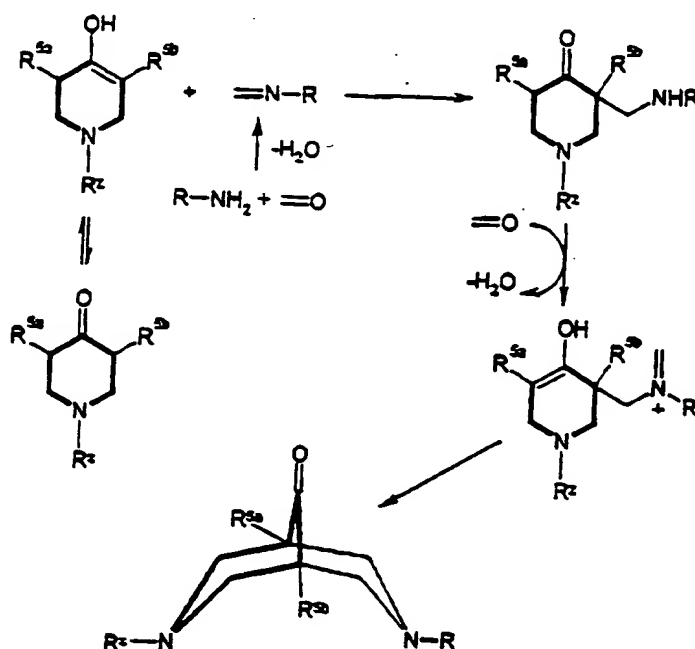


XXX

or a protected derivative thereof, wherein R^4 , R^6 , A, B and D are as defined in Claim 1, in the presence of a formaldehyde.

27 (previously presented). A method as claimed in Claim 20, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

R^3 represent methyl. It is important to understand the chemistry involved in the processes of claim 26. Thus, first, the substituents R^2 and R^3 are not present in compounds with formulae VIII and XVII, which are bispidone derivatives. Secondly, the formaldehyde is incorporated into the part of the bispidine ring system that is unsubstituted, as set out in the reaction scheme below:



Withdrawal of the rejection set forth in paragraph 7 is now believed to be in order, and is requested.

With reference to paragraph 8, the Examiner alleges that claim 21 is improperly dependent on claim 1, as it is believed that the bispidine *N*-oxide and quaternary ammonium salts are not protected forms of compounds of formula I, as defined in claim 1. In response, claim 21 is not dependent upon claim 1, as it relates to processes and

not compounds. This point is discussed earlier in this response. However, in order to further clarify the claims, claim 1 has been amended to include *N*-oxide and C₁₋₄ alkyl quaternary ammonium derivatives of compounds of formula I (see page 8, lines 1-7 of the application as originally filed).

Withdrawal of the outstanding 35 U.S.C. § 112, second paragraph, rejection is now believed to be in order. Such action is respectfully requested.

II. THE 35 U.S.C. § 112, FIRST PARAGRAPH, REJECTIONS

Claim 21 stands rejected under 35 U.S.C. § 112, first paragraph, on alleged lack of enablement grounds with respect to the scope of (r). In response, and without conceding to the merit of that rejection, (r) has been cancelled without prejudice.

Withdrawal of the 35 U.S.C. § 112, first paragraph, rejection in regard to the scope of (r) is now respectfully requested.

Claims 1-14 and 20-26 stand rejected under 35 U.S.C. § 112, first paragraph, on alleged lack of enablement grounds with respect to solvates. Without conceding to the merit of this rejection, the claims have been amended to remove reference to "solvates". Withdrawal of this rejection is now respectfully requested.

III. DOUBLE PATENTING

Claims 1-14 and 20-27 stand rejected on alleged obviousness-double patenting grounds over claims 1-26 of copending application Serial No. 09/623,705. Without conceding to the merit of this rejection a Terminal Disclaimer executed by the undersigned was submitted with the response dated November 8, 2002, together with the requisite fee. Withdrawal of this rejection is now respectfully requested.

IV. THE ADVISORY ACTION

In response to the Advisory Action mailed June 20, 2003, the claims have been amended without prejudice to include the carbon ranges for the cycloalkyl and cycloalkoxy moieties. These ranges correspond to the alkyl ranges, with the exception that the lower carbon number is three (basis appears at page 9, line 1). No new matter is entered.

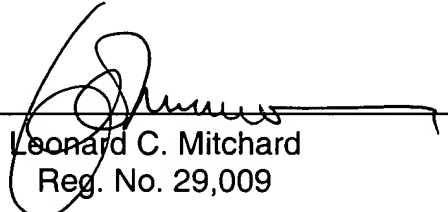
Step (r) in claim 21 has been canceled without prejudice. This overcomes the rejection of claims 22-24.

Allowance of the application is awaited.

Respectfully submitted,

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By: _____


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